

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Sabine FRICKE

Group Art Unit: 1617

Serial No.: 10/798,780

Examiner: San Ming HUI

Filed: March 12, 2004

For: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR RELIABLE  
ACHIEVEMENT OF ACCEPTABLE SERUM TESTOSTERONE LEVELS

**DECLARATION UNDER 37 C.F.R. §1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

I, Dr. Sabine Fricke, being duly warned, declare that:

I am a citizen of Germany, residing in Jena, Germany.

I am the same person who submitted a declaration in this application which I executed on January 15, 2008. This declaration relates to the same data but clarifies the nature of that data, particularly clarifying that the amounts of castor oil and benzyl benzoate in the vehicle were in weight%.

I am an inventor of the above-captioned application and am, therefore, familiar with the invention described therein and with the grounds for rejection made against the claims by the U.S. Patent and Trademark Office. My expertise for making this declaration is further demonstrated in the CV attached to my previous declaration.

If a patent issues from this application and if it is decided by the assignee to pursue a

commercial product falling under its claims and if such a commercial product is approved by FDA and sold in the US, then under German law, I and the other inventors will receive some remuneration derived from such sales.

The experiments described herein were conducted by me or under my supervision.

Experiments were conducted to assess the solubility of testosterone undecanoate (TU) in different oils. Different benzyl benzoate/oil mixtures that contained 250 mg TU per ml were studied as to their crystallizability in a refrigerator (at 2-8°C). It was to be determined which particular oil and which ratio of concentrations of benzyl benzoate/oil had the highest TU-dissolving capacity.

#### Materials

Refined castor oil for parenteral use: DAB [*German Pharmacopoeia*]

Peanut oil for parenteral use: Ph. Eur.

Miglyol 812: Ph. Eur.

Benzyl benzoate: Ph. Eur., USP

Testosterone undecanoate: Internal Monograph

#### Preparation

To prepare each of the test solutions, 25 g TU were dissolved at 50°C in the respective amount of benzyl benzoate, whereupon the amount of the respective oil was added. The resultant mixture was then stirred. A clear solution had to be formed. Ampoules were each filled with 4 ml of part of the solution and then closed. Eight of the closed ampoules were kept in a refrigerator (at 2-

8°C) and 4 ampoules were kept at 25°C. The ampoules were checked at specific times for the presence of any precipitate (crystals).

**Mixing ratios:**

25 g TU in a mixture of 40 weight% benzyl benzoate + 60 weight% refined castor oil

25 g TU in a mixture of 50 weight% benzyl benzoate + 50 weight% refined castor oil

25 g TU in a mixture of 63 weight% benzyl benzoate + 37 weight% refined castor oil

25 g TU in a mixture of 40 weight% benzyl benzoate + 60 weight% peanut oil

25 g TU in a mixture of 50 weight% benzyl benzoate + 50 weight% peanut oil

25 g TU in a mixture of 63 weight% benzyl benzoate + 37 weight% peanut oil

25 g TU in a mixture of 40 weight% benzyl benzoate + 60 weight% Miglyol 812

25 g TU in a mixture of 50 weight% benzyl benzoate + 50 weight% Miglyol 812

25 g TU in a mixture of 63 weight% benzyl benzoate + 37 weight% Miglyol 812

**Conversion:**

For the above three mixtures of benzyl benzoate and refined castor oil, respectively, the following conversions into vol% (based on a density for benzyl benzoate of 1.12 g/cm<sup>3</sup> and a density for refined castor oil of 0.958 g/cm<sup>3</sup>) are provided:

25 g TU in a mixture of 36.3 vol% benzyl benzoate + 63.7 vol% refined castor oil

25 g TU in a mixture of 46.1 vol% benzyl benzoate + 53.9 vol% refined castor oil

25 g TU in a mixture of 59.3 vol% benzyl benzoate + 40.7 vol% refined castor oil

**Results:**

Stability of the oily solutions at room temperature (25°C). The solutions were considered stable if there was exhibited no precipitate (crystals) in the ampoule after 34 days time. The data are shown in the attached table. The only solution which maintained sufficient solubility in the tests was a solution containing TU in a 37 weight% (40.7 vol%) castor oil and 63 weight% (59.3 vol%) cosolvent oily solution.

The data demonstrate that castor oil is surprisingly advantageous to other oils for providing a stable solution of TU. Further, the data demonstrate that castor oil is surprisingly advantageous when used in a lower concentration relative to the cosolvent, as opposed to higher concentrations previously thought to be necessary.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

25. Mai 2005  
Date

Sabine Fricke  
Dr. Sabine Fricke

# Stability of the oily solutions during storage in a refrigerator (at 2-8 °C)

Formulations containing refined castor oil for parenteral use	Number of ampoules with precipitation (crystals) after										
	0 d	1 d	2 d	3 d	6 d	8 d	10 d	21 d	34 d		
40% benzyl benzoate	0	5	6	6	6	6	6	6	6		
50% benzyl benzoate	0	0	1	3	3	3	3	4	5		
63% benzyl benzoate	0	0	0	0	0	0	0	0	0		

Formulations containing peanut oil for parenteral use	Number of ampoules with precipitation (crystals) after										
	0 d	1 d	4 d	6 d	8 d	19 d	32 d				
40% benzyl benzoate	0	5	6	6	7	8	8				
50% benzyl benzoate	0	2	5	5	5	7	8				
63% benzyl benzoate	0	0	5	5	5	7	8				

Formulations containing Miglyol 812 for parenteral use	Number of ampoules with precipitation (crystals) after										
	0 d	1 d	2 d	5 d	7 d	9 d	20 d	33 d			
40% benzyl benzoate	0	4	4	7	8	8	8	8			
50% benzyl benzoate	0	1	1	8	8	8	8	8			
63% benzyl benzoate	0	0	1	1	1	1	5	6			

It can be said in conclusion that the formulation that contains refined castor oil for parenteral use with a percentage of 63% benzyl benzoate (= composition of the original Nebido®-formulation) is the only formulation in which TU does not precipitate during storage over 34 days in a refrigerator (at 2-8°C). All other tested oils and, respectively, mixing ratios give an unstable product.